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REVIEW ARTICLE

Invasive *Aspergillus* Sinusitis in Human Immunodeficiency Virus Infection: Case Report and Review of the Literature

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Invasive *Aspergillus* (IA) sinusitis is a life-threatening opportunistic infection in immunocompromised individuals, but it is uncommon in human immunodeficiency virus (HIV) infection. To gain a better understanding of the characteristics of IA sinusitis in this population, we present a unique case of chronic IA sinusitis in an HIV-infected patient taking antiretroviral therapy and review the literature summarizing published cases of invasive aspergillosis of the paranasal (n = 41) and mastoid (n = 17) sinuses in HIV-infected individuals. Among these cases, only 4 were reported after 1999, and 98% of patients had acquired immune deficiency syndrome. Orbital invasion occurred in 54% of paranasal sinus cases, whereas intracranial invasion was reported in 53% of mastoid sinus cases. The overall mortality was 79%. We also discuss various clinical and immunologic factors that may play a role in the development of IA and consider the changing epidemiology of aspergillosis in the era of effective antiretroviral therapy.

Keywords. AIDS; *Aspergillus*; HIV; invasive fungal sinusitis; opportunistic infection.

Invasive aspergillosis (IA) is a rare and life-threatening opportunistic infection that occurs predominantly in immunocompromised hosts [1]. Neutrophil disorders are established risk factors for IA—often the consequence of diseases such as diabetes, primary immune deficiencies, hematologic neoplasms, stem cell or solid organ transplantation, or the receipt of chemotherapy or corticosteroids [2, 3]. Over the years, advanced human immunodeficiency virus (HIV) infection has emerged as a risk factor for IA along with other invasive fungal infections such as *Pneumocystis* pneumonia, cryptococcal meningitis, esophageal candidiasis, and disseminated histoplasmosis [4–6]. These diseases predominate in those with low CD4 cell counts, nonsuppressed HIV ribonucleic acid (RNA) levels, and in those not receiving antiretroviral therapy (ART) [4]. Indeed, despite the increased availability of effective ART since 1999, invasive fungal infections remain a major cause of global HIV-related mortality [7].

However, despite the multiple invasive fungal infections that characterize acquired immunodeficiency syndrome (AIDS) and the nearly inevitable exposure to *Aspergillus* spores in the environment, IA remains uncommon in the HIV population [5, 8]. Moreover, fewer than 3% of IA cases occur in those infected with HIV [2, 9]. When also considering that approximately 80% of IA cases in HIV-infected individuals are pulmonary infections, understanding the features of IA in less common sites such as the paranasal and mastoid sinuses becomes a challenge [4–6, 9, 10].

To address this challenge, we present a unique case and review of the literature describing reported cases of IA of the paranasal and mastoid sinuses in HIV-infected individuals. We examine the clinical features of IA sinusitis, highlight recent scientific insights about the pathogenesis and risk of IA in the context of HIV, and discuss the changing epidemiology of IA in the era of effective ART.

METHODS

A search for published cases of IA sinusitis in HIV-infected people was conducted in PubMed and Embase using the keywords "aspergillus", "invasive", "fungus", "sinus", "mastoid", and terms encompassing HIV infection. Only cases in which imaging confirmed invasive sinusitis and *Aspergillus* was documented by histopathologic exam or culture were included in the review [1]. Extracted data included case year, age, sex, ART regimen, immune parameters (CD4 cell count, HIV RNA level, and AIDS diagnosis as defined by a reported CD4 < 200 cells/mm^3 or AIDS-defining condition according to the current Centers for Disease Control and Prevention criteria), risk factors for IA and opportunistic infections, medications, involved sinuses, invasive sites, surgical and antifungal treatments, and outcome.

CASE

A 47-year-old woman with a history of AIDS (most recent CD4 214 cells/mm^3) and advanced HIV-associated dementia presented in November 2013 with a frontal headache and a month-long decline in cognitive and functional ability. She was diagnosed with AIDS in 1996 after developing cachexia but had no known history of other opportunistic infections. She was taking tenofovir, emtricitabine, and lopinavir with

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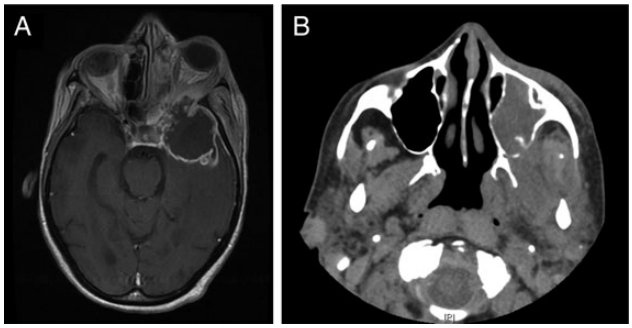

Figure 1. Magnetic resonance imaging (A) and computed tomography scan (B) demonstrating left maxillary sinusitis with invasion through the posterior maxillary wall into the intracranial fossa, orbit, cavernous sinus, and foramen ovale.

ritonavir, and her HIV RNA was <50 copies/mL. She was not taking any prophylaxis for opportunistic infections at the time of presentation. On physical exam, she was afebrile with normal vital signs. Proptosis and ophthalmoplegia of the left eye were present. Laboratory results included a white blood cell count of 13 100 cells/mm^3 (72% neutrophils) and normal chemistry and liver panels. Computed tomography (CT) and magnetic resonance imaging (MRI) scans demonstrated an opacified left maxillary sinus with a $3 \times 3 \times 3$ cm mass in the left cranial fossa (Figure 1). This mass extended into the orbit, cavernous sinus, and foramen ovale. A chest x-ray showed no evidence of possible pulmonary aspergillosis. A transnasal biopsy of the mass in the infratemporal fossa identified hyphae consistent with *Aspergillus* and fungal culture grew *Aspergillus fumigatus*. Serum (1→3)-β-D-glucan was positive (167 mg/mL), and galactomannan antigen enzyme immunoassay was also positive (index 2.31). Intravenous voriconazole and micafungin were administered for 6 weeks, and the patient was thereafter transitioned to oral voriconazole alone. Raltegravir was substituted for lopinavir/ritonavir given their potential for drug interaction with voriconazole. Surgery was not attempted given the patient's underlying poor cognitive and functional status and the already extensive invasion of the mass. A repeat MRI performed 3 months after initiating antifungal therapy showed no significant change in the size of the mass. She remains alive at the time of writing, now 30 months after presentation, with CD4 591 cells/mm^3 and HIV RNA <20 copies/mL and without significant clinical decline.

RESULTS

We identified 36 articles containing 58 cases of invasive *Aspergillus* sinusitis (41 paranasal and 17 mastoid cases) in patients with HIV infection from 1991 to the present. These cases are summarized in Table 1 (paranasal) and Table 2 (mastoid).

Among 42 cases of IA of the paranasal sinuses (including our case), only 4 were reported after 1999 (Table 3). Ninety-eight percent of cases occurred among individuals with AIDS, and 95% were due to *A fumigatus*. Overall, neutrophil disorders were identified in 45% of cases, including neutropenia (32%), corticosteroid use (16%), or receipt of chemotherapy (8%). The maxillary and ethmoid sinuses were the most commonly involved sinuses, whereas multisinus involvement was reported in 77% of cases. The orbit was the most commonly invaded structure (54%). Approximately 80% received amphotericin B and surgery. However, the mortality was 80%.

Among a total of 17 cases of *Aspergillus* mastoiditis, none were reported after 1999 (Table 4). All cases occurred among individuals with AIDS, and all were due to *A fumigatus*. Neutropenia was reported in only 18% of evaluable cases, whereas recurrent otitis media or chronic otitis externa was present in 55%. Facial nerve palsy occurred in 60%, and invasion of the temporal lobe and cerebellum occurred in 29% and 18%, respectively. Eighty-seven percent of patients underwent some surgical procedure, and 75% received amphotericin B. The overall mortality was 73%.

DISCUSSION

Invasive *Aspergillus* of the paranasal and mastoid sinus is an uncommon but frequently lethal disease in individuals with HIV infection. Only 4 of 58 cases summarized in our review occurred after 1999, likely reflecting the more common occurrence of IA sinusitis before the widespread availability of ART. However, our case illustrates that IA may still occur in individuals on effective ART without advanced HIV immunosuppression, warranting that clinicians remain aware of the spectrum of IA and its evolving management in HIV infection.

Disorders of neutrophil number or function are central risk factors for IA in immunocompromised populations regardless of the presence of HIV infection [1, 5, 6, 44]. In our review, the prevalence of neutropenia among paranasal sinus cases was 32% and 18% among mastoiditis cases (Tables 3 and 4). In other series of HIV-infected patients with predominantly pulmonary IA, neutropenia prevalence ranged from 13% to 51% [6, 36, 44]. Medications known to cause neutropenia (eg, ganciclovir, trimethoprim-sulfamethoxazole, zidovudine, and cancer chemotherapy) or those that may be markers for neutropenia (eg, granulocyte colony-stimulating factor) were also reported in 37% of paranasal sinus cases in our series. Similar findings have been reported previously [5], although whether such medications contribute to the risk of IA directly (via drug-induced neutropenia) or indirectly (as indicators of bone marrow disruptive diseases) is not known. Corticosteroid use, particularly when prolonged, deleteriously affects neutrophil migration and was reported in 16% of paranasal sinus cases [2, 5].

A prior diagnosis of AIDS-related opportunistic infections (AIDS-OIs) was also present in over 70% of paranasal and mastoid cases in our series. This reflects severe immunodeficiency and can also be associated with receipt of neutropenia-causing medications [5]. However, the direct immune-modulating

Table 1. Reported Cases of Invasive Aspergillosis of the Paranasal Sinuses in Individuals With HIV Infection (n = 42)

Year[a]	Age	Sex	CD4[b]	ART	Medical Comorbidity, OIs, and Risk Factors	*Aspergillus* Species	Signs and Symptoms	Sinus Involved[c]	Site of Invasion	Surgery	Antifungal	Outcome and Comments	Ref.
1991	29	M	8	n/a	PCP, CMV colitis and pneumonitis, pulmonary TB, chronic sinusitis with prior sinus surgery	*Aspergillus fumigatus*	Periocular pain, lid swelling, diplopia, proptosis	Mx, E, (bilat)	E→orbit	Orbitotomy with debridement, maxillary washout	AmB	death (2 mo)	[11]
1991[a]	44	M	AIDS	n/a	PCP, HIV cardiomyopathy	*A fumigatus*	Fever, headache, difficulty walking, hemiparesis	S	Suprasella area, epidura, brainstem	no	no	death (<1 wk due to cardiac arrest)	[12]
1991[a]	n/a	M	AIDS	n/a	PCP, neutropenia, corticosteroids, concurrent pulmonary aspergillosis	n/a	n/a	P	cerebrum	Caldwell-Luc[d]	AmB	death (10 d)	[10]
1992[a]	32	F	AIDS	n/a	n/a	*A fumigatus*	Facial swelling, proptosis, eye pain, lid erythema, exopthalmos	E	orbit	transorbital ethmoidectomy	AmB (local and systemic)	n/a	[13]
1992[a]	32	M	AIDS	n/a	AIDS wasting, isosporiasis, ANC >2000 cells/mm^3	*A fumigatus*	n/a	Mx	frontal lobe	Caldwell Luc, transantral ethmoidectomy	AmB	death (due to isosporiasis and sepsis	[6]
1993	n/a	M	10	ddI	PCP, KS, CMV-R, cryptosporidiosis, ANC 600 cells/mm^3	*A fumigatus*	n/a	Mx	n/a	n/a	Itra	n/a; concurrent laryngeal involvement	[14]
1993[a]	36	M	AIDS	n/a	CNS toxo, MAI, CMV-R, gancyclovir, neutropenia, corticosteroids	n/a	Facial swelling, exopthalmos, lid erythema	Mx, F	retro-orbital space, intracranial	no	AmB, Itra	death ("few weeks")	[15]
1993	30	M	5	ZDV	MAC, disseminated VZV, PCP, acyclovir, TMP/SMX, ANC 900 cells/mm^3	*A fumigatus*	Facial swelling, fever, facial pain, facial erythema	Mx, E, S, F	S→ intracranial	debridement	AmB, Itra	death (2 d after surgery due to heart failure)	[16]
1993	38	M	8	n/a	CMV-R, MAC, recurrent oral candidiasis, chronic sinusitis, marijuana, ANC 600 cells/mm^3	*A fumigatus*	Fever, facial pain, headache	Mx, E, (bilat) → Pansinus	M→ intracranial	bilat. ethmoidectomy, Caldwell-Luc, nasal antral window	Itra × 6 wk	death (5 mo)	[17]
1994[a]	50	M	30	n/a	CMV-R, MAC, KS, lymphoma, chemotherapy, corticosteroids, ANC 120 cells/mm^3	*A fumigatus*	Fever, decreased vision, seizure	F, Mx, E (bilat)	frontal lobe	resection of frontal lobe abscess	AmB	death (2 d after surgery due to brain herniation)	[17]
1994[a]	33	M	<10	n/a	KS, chemotherapy	*A fumigatus*	Fever, periorbital swelling	F, Mx, E (bilat)	frontal lobe, orbital apex, optic nerve	fronto-ethmoidectomy and orbitectomy with debridement	AmB (local and systemic)	death (<1 wk)	[17]
1994	35	F	20	ZDV, ddC	History of neutropenia (wbc 500–3000 cells/mm^3 the past year), corticosteroids	*A fumigatus*	Fever followed by decreased vision, diplopia, rhinorrhea, facial pain; CNV and CNVI palsy	Mx (bilat), E	orbit, temporal lobe, cavernous sinus, pterygopalatine fossa	L temporal craniotomy with debridement	AmB (systemic, intrathecal), terbenafine, Itra	Death (9 mo)	[18]
1994[a]	30	M	AIDS	n/a	n/a	*A fumigatus*	Proptosis, decreased vision, diplopia (CNVI palsy)	E	Orbit	no	AmB (local and systemic)	death (3 mo)	[19]
1994[a]	42	M	10	n/a	G-CSF	*A fumigatus*	n/a	Mx (bilat), S, F	F→frontal lobe	yes	AmB (local and systemic), Itra	death (~10 wk)	[20]
1994	37	M	n/a	n/a	Alcoholic cirrhosis	*A fumigatus*	CNIII and CNVI palsy, decreased vision, eye pain, headache	Mx, S (bilat)	S→orbital apex	Debridement	AmB	death (2 wk)	[21]
1995[a]	35	M	11	n/a	MAC, TB, CMV, candida esophagitis, ANC 1900 cells/mm^3	*A fumigatus*	eye and ear pain, CNVII palsy, jaw swelling, headache, dizziness, nausea, hemorrhagic otorrhea, eye pain	Pansinus	L temporal lobe; R frontal lobe	No	AmB, Itra	death (3 mo)	[3]
1995[a]	37	M	34	n/a	TMP/SMX	*A fumigatus*	Decreased vision	S	sella turcica→ intracranial	yes	AmB (local and systemic)	death (5 d after surgery)	[22]
1995[a]	45	M	<50	None	PCP, CMV-R, MAC; ANC 1440 cells/mm^3	*A fumigatus*	Fever, rhinorrhea, facial pain, headache	Pansinus	M→infrazygomatic masticator space, temporal fossa	Caldwell-Luc	AmB, Itra	death (9 wk)	[3]
1995	45	M	<50	Salvage regimen	PCP, MAC, AIDS wasting, corticosteroids, TMP/SMX, gancyclovir, Itra prophylaxis	*A fumigatus*	fever, decreased vision, headache	(bilat)	S→optic chiasm	debridement	AmB	death (2 wk after surgery)	[23]

Table 1 continued.

Year[a]	Age	Sex	CD4[b]	ART	Medical Comorbidity, OIs, and Risk Factors	*Aspergillus* Species	Signs and Symptoms	Sinus Involved[c]	Site of Invasion	Surgery	Antifungal	Outcome and Comments	Ref.
1995	36	M	0	n/a	KS, ANC 1000 cells/mm^3	*A fumigatus*	Fever, nasal discharge, headache	E, Mx	E→pterygopalatine fossa	Caldwell-Luc	AmB	Death, 1 mo after surgery	[24]
1996[a]	24	M	AIDS	n/a	Hemophelia, molluscum contagiousum, oral candidiasis	*A fumigatus*	n/a	E, S, Mx	E→orbit (via cribriform plate)	debridement	AmB	death (3.5 mo)	[11]
1996[a]	35	F	1	n/a	PCP	*A fumigatus*	n/a	E (bilat), F, Mx	epidura	debridement	AmB	alive (9 mo follow-up)	[11]
1996[a]	33	F	10	n/a	None	*A fumigatus*	n/a	E, S, F, Mx (bilat)	E→cribriform plate (orbit)	debridement	AmB	death (1 y)	[11]
1996	38	M	12	SQV, d4T, 3TC	CMV-R, lymphoma, marijuana	*A fumigatus*	Proptosis, epistaxis, CNIII palsy	E, F, S, Mx	orbit, frontal lobes	ethmoidectomy, frontal and sphenoid sinusotomy, orbitotomy with multiple debridements	AmB, Itra	death (28 mo)	[25]
1996	12	F	49	PI-based triple therapy	Lymphoma, cryptococcal meningitis, CMV-R, gancyclovir	*A fumigatus*	n/a	E, S, Mx (bilat)	orbit, cavernous sinus, middle cranial fossa, temporal lobe	debridement	AmB, Itra	death (8 mo)	[26]
1997[a]	39	M	0	None	CMV-R, gancyclovir, TMP/SMX, clarithromycin, G-CSF, recurrent sinusitis	*A fumigatus*	n/a	n/a	nasal septum	multiple debridements	AmB, Itra	alive (1 y)	[23]
1997[a]	39	M	<10	n/a	CMV-R, MAC, PCP, ganciclovir, history of neutropenia, current ANC 1170 cells/mm^3	*A fumigatus*	Facial pain, fever, periorbital swelling	E, S	orbit	Caldwell-Luc, ethmoidectomy, sphenoidectomy	AmB	death (2 wk)	[27]
1997	34	F	37	n/a	CMV-R, PCP, marijuana	*A fumigatus*	Nasal congestion, proptosis, facial pain, headache, eye pain	E	orbit	ethmoidectomy, frontal sinusotomy and orbital decompression	AmB	alive	[25]
1997	34	F	4	n/a	CMV-R, PCP, ANC 900 cells/mm^3	*A fumigatus*	diplopia, decreased vision, proptosis, L ophthalmoplegia	S (bilat), E	S→ orbital apex, cavernous sinus	debridement	AmB	death (8 d after surgery)	[24]
1997	45	M	10	Salvage regimen	PCP, MAC, AIDS wasting, corticosteroids, clarithromycin, gancyclovir, TMP/SMX, Itra (for refractory oral candidiasis)	*A fumigatus*	Fever, headache, decreased vision, bitemporal hemianopia	P, S	optic chiasm	sinus debridement	AmB	death (2 wks)	[18]
1997	13	F	AIDS	ZDV, ddI, PI	chronic sinusitis, prior sinus surgery, myelodysplastic syndrome, Burkitt's lymphoma, neutropenia, G-CSF, chemotherapy, concurrent pulmonary aspergillosis	*A fumigatus*	Headache, vision loss, proptosis, left extremity weakness	P	orbit, temporal lobe, basal ganglia	no	voriconazole	death (2 mo)	[26]
1998[a]	43	F	n/a	n/a	n/a	*A fumigatus*	Facial pain, headache	Mx	orbit	debridement	AmB	n/a	[28]
1999[a]	34	M	29	ZDV, ddI	CNS toxo, cryptosporidium, AIDS wasting, ANC 760 cells/mm^3	*A fumigatus*	Facial pain, headache, CNV sensory loss, CNVII palsy	E, S	orbit, cavernous sinus	debridement	AmB, Itra	alive (14 mo)	[29]
1999[a]	38	M	10	PI-based triple therapy	CMV-R (on gancyclovir, which caused neutropenia), MAI, pulmonary TB	*A fumigatus*	Fever, sinus congestion	Mx	lysis of hard palate and intersinonasal wall	Caldwell-Luc	AmB, Itra	alive (>6 mo follow-up)	[29]
1999[a]	52	M	0	ZDV, d4T	KS	*A fumigatus*	Headache	F, E, Mx,	intracerebral extension to epidura	Caldwell-Luc	AmB, Itra	death (4 mo)	[29]
1999[a]	32	F	10	n/a	PCP, MAC, cryptococcal meningitis, cutaneous VZV with ophthalmicus, marijuana	*A fumigatus*	Proptosis, decreased vision, headache, n/v, L affarent pupillary defect, L optic disc swelling	E, S (bilat.)	orbit, frontal lobe	ethmoidectomy, sphenoid and frontal sinusotomy, orbital decompression, debridement	AmB (local and systemic)	death (14 mo)	[25]
1999[a]	31	M	11	n/a	PCP	*A fumigatus*	facial swelling, fever, proptosis, decreased vision, facial pain, epistaxis	E, S, Mx (bilat)	orbit, frontal lobes	bilateral ethmoidectomies, maxillary, frontal, and sphenoid sinusotomies, and orbital and intracranial decompression	AmB	death (2 wk)	[25]
1999[a]	35	F	1	n/a	Chronic sinusitis	*A fumigatus*	Fever, proptosis	E (bilat), F, Mx	bilateral frontal lobes, right orbit	debridement	AmB (local and systemic)	death (7 mo)	[25]
2007[a]	41	M	8	n/a	PCP, MAC, chronic sinusitis	n/a	Recurrent epistaxis, sinus congestion	S	cavernous sinus and internal carotid artery	no	n/a	death (2 y due to AIDS-related complications)	[30]

Table 1 continued.

Year[a]	Age	Sex	CD4[b]	ART	Medical Comorbidity, OIs, and Risk Factors	*Aspergillus* Species	Signs and Symptoms	Sinus Involved[c]	Site of Invasion	Surgery	Antifungal	Outcome and Comments	Ref.
2009	39	F	395	TDF, FTC, RAL	Polypectomy for recurrent nasal polyps 2 y prior	*Aspergillus flavus*	Proptosis, epiphora	Mx, E, F (bilat)	pituitary fossa, orbit	debridement	voriconazole	alive (12 mo follow-up)	[31]
2011[a]	n/a	n/a	AIDS	n/a	n/a	*A flavus*	n/a	n/a	R middle meatus, nasal septum	debridement	n/a	alive (13 mo)	[32]
2013	47	F	214	TDF, FTC, LPV/r	HIV-associated dementia	*A fumigatus*	Headache, worsening dementia, proptosis, opthalmoplegia	n/a	orbit, cavernous sinus, foramen ovale	no	voriconazole, micafungin	alive (28 mo)	case

Abbreviations: AIDS, acquired immune deficiency syndrome; AmB, amphotericin B; ANC, absolute neutrophil count; ART, antiretroviral therapy; bilat., bilateral; CMV, cytomegalovirus; CMV-R, CMV retinitis; CNS toxo, central nervous system toxoplasmosis; CNV, cranial nerve 5; CNVII, cranial nerve 6; CNVII, cranial nerve 7; ddC, zalcitabine; ddI, didanosine; d4T, stavudine; E, ethmoid; F, frontal; FTC, emtricitabine; G-CSF, granulocyte colony-stimulating factors; HIV, human immunodeficiency virus; Itra, itraconazole; KS, Kaposi sarcoma; LPV/r, lopinavir/ritonavir; M, mastoid; MAC, disseminated *Mycobacterium avium* complex; MAI, disseminated *M avium-intracellulare*; Mx maxillary; n/a, not available in report; OI, opportunistic infection; P, paranasal sinus; PCP, pneumocystis pneumonia; PI, protease inhibitor; RAL, raltegravir; S, sphenoid; SQV, saquinavir; TB, tuberculosis; TDF, tenofovir; TMP/SMX, trimethoprim/sulfamethoxazole; TM, tympanic membrane; VZV, varicella-zoster virus; wbc, white blood cell count; ZDV, zidovudine.

[a] Indicates year of publication when year of case not reported.

[b] CD4 cell count in cells/mm^3; "AIDS" listed when specified in report and when CD4 cell count not reported.

[c] Sinus involved (based on radiographic imaging).

[d] Caldwell-Luc procedure involves surgically draining the maxillary sinus via a fenestration created at the anterior wall of the sinus.

effects of AIDS-OIs themselves may also play a role. Cytomegalovirus disease, present in 35% of paranasal sinus cases, has been suggested as a risk factor for IA in hematopoietic cell transplant recipients independent of ganciclovir-induced neutropenia, possibly due to viral infection of hematopoietic cell precursors [45]. Bone marrow infiltrative conditions common in AIDS, such as disseminated *Mycobacterium avium-intracellulare* or lymphoma, were also reported in multiple cases and may contribute similar risk, although, notably, IA remains uncommon even with these conditions.

Finally, a history of chronic or recurrent otitis media or otitis externa was reported in 55% of mastoiditis cases and reflect the common spectrum of associated diseases of the middle ear and/or mastoid air cell tract. Chronic sinusitis and associated antibiotic treatment (predisposing to fungal colonization), prior surgery, and marijuana use (potentially increasing exposure to *Aspergillus*) were also reported in 8%–16% of paranasal sinus cases, although they remain as less-established risk factors for IA sinusitis.

Although the presence of certain symptoms and signs in the appropriate host should alert clinicians to suspect IA sinusitis, the absence of such features should not preclude consideration of the disease in an individual with advanced HIV infection. Indeed, aggressive infection may ensue with few symptoms in patients with neutropenia or a profoundly compromised inflammatory response, manifesting as acute or subacute IA in the vast majority of patients in our review. However, disease progression may be protracted or chronic in those with less profound immunosuppression [2]. Indeed, only our case and 1 other case in our review had CD4 > 200 cells/mm^3, and both remained alive after 12 months follow up [31]. This illustrates the critical influence of host immunity in the rate of clinical progression of IA.

Bacterial infection of the paranasal sinus or external/middle ear may also precede *Aspergillus* colonization and invasion of the paranasal or mastoid sinus, causing similar symptoms as IA. This transition may be clinically indiscernible and may in part account for the broad duration of symptoms ranging from days to months observed among the cases in our review. Moreover, bacterial pathogens are more common causes of sinusitis than *Aspergillus* across all stages of HIV infection, although they are less likely to cause invasive disease [22, 39, 46, 47]. Sinonasal mucormycosis is also clinically indistinguishable from *Aspergillus*, and it warrants the empiric use of amphotericin B until the causative pathogen is confirmed [1, 46, 47]. In the patient with advanced HIV infection, additional etiologies include *Cryptococcus* [48], *Candida* [49], *Scedosporium* [50], nontuberculous mycobacteria [22], and malignancies such as non-Hodgkin's lymphoma [51].

In our review, fever, headache, and pain around the face or eye were the most common symptoms of paranasal sinus IA and were each present in approximately 40% of cases. The orbit was the most common site of invasion (53%) and manifested with a

Table 2. Reported Cases of Invasive *Aspergillus* Mastoiditis in Individuals With HIV Infection (n = 17)

Year[a]	Age	Sex	CD4[b]	ART	Medical Comorbidity, OIs and Risk Factors	*Aspergillus* Species	Signs and Symptoms	Site of Invasion	Surgery	Antifungal	Outcome & Comments	Ref.
1987	21	F	AIDS	ZDV	CMV-R, MAI, TMP/SMX, and acyclovir	*Aspergillus fumigatus*	nasal congestion, hearing loss, otalgia, mastoid swelling	cerebellum, temporal lobe	catheter drainage only	AmB	death (4 mo after drainage procedure)	[33]
1990	30	M	AIDS	ZDV	candida esophagitis, recurrent OM	*A fumigatus*	hearing loss, otalgia, purulent otorrhea	temporal bone	no	AmB, Itra	death (8 mo, attributed to CNS toxo and *Pseudomonas* sepsis)	[34]
1990	42	M	AIDS	ZDV	KS, candida esophagitis, recurrent OM	*A fumigatus*	CNVII palsy (recovery unknown)	temporal bone	mastoidectomy, debridement	Am, Itra	alive (7 mo)	[34]
1991[a]	27	F	AIDS	n/a	neutropenia, recurrent OM	*A fumigatus*	otalgia, otorrhea TM perforation, CNVII palsy (post-surgery, recovery unknown)	transverse sinus, temporal lobe, cerebellum, brainstem	mastoidectomy	AmB × 4 d, Itra	death (6 mo); Invasion noted after mastoid debridement	[35]
1991[a]	27	M	AIDS	ZDV	n/a	*A fumigatus*	fever, headache, rhinorrhea, otalgia, tinnitus, hearing loss	mastoid only	mastoidectomy	clotrimazoleotic drops	alive (up to 12 mo f/u)	[35]
1993[a]	39	F	AIDS	ZDV	CMV-R, neutropenia	*A fumigatus*	fever, hearing loss, otalgia	mastoid only	mastoidectomy	AmB × 4 wk, Itra × 13 wk	death (4 mo)	[36]
1993[a]	24	M	AIDS	ZDV	chronic OM	*A fumigatus*	otorrhea, CNVII palsy, fever, chills, headache	cerebellum, lateral sinus thrombosis	mastoidectomy, debridement	AmB	n/a; bilateral TM tubes placed 6 wk before onset of symptoms	[37]
1995[a]	39	M	15	n/a	PCP, MAI, chronic otitis externa; ANC 1885 cells/mm^3	*A fumigatus*	headache	temporal lobe	mastoidectomy	AmB, Itra	death, 12 wk	[3]
1996	27	F	1	n/a	candida esophagitis, CMV-R (w/history of leukopenia), disseminated CMV, ANC >2000 cells/mm^3	*A fumigatus*	otalgia, CNVII palsy (no recovery)	temporal lobe epidura	no	Itra, AmB	death (3 mo, AmB was started only 1 week before death	[38]
1997[a]	41	M	AIDS	n/a	n/a	*A fumigatus*	n/a	intracranial, masticator space, parapharyngeal space, infratemporal area, nasopharynx, eustacean tube, contralateral side	n/a	none	death	[39]
1997[a]	18	M	AIDS	n/a	hemophilia, recurrent OM	*A fumigatus*	fever, otalgia, hearing loss, impaired facial sensation	mastoid only	mastoidectomy	Itra	death (2 wk after surgery for gastrointestinal hemorrhage)	[40]
1999[a]	27	F	1	n/a	candida esophagitis, CMV-R, WBC > 2000 cells/mm^3, PCP, CMV pneumonitis	*A fumigatus*	otalgia, mastoid pain and swelling, CNVII palsy (no recovery)	masticator space, temporal lobe epidura	no	Itra	death (3 mo after diagnosis due to respiratory illness)	[41]
1999[a]	41	M	18	n/a	PCP, TMP/SMX	*A fumigatus*	otalgia, otorrhea, hearing loss, CNVII palsy (recovery after 1 mo)	mastoid only	mastoidectomy	AmB, Itra	alive (3 mo after surgery)	[42]

Table 2 continued.

Year[a]	Age	Sex	CD4[b]	ART	Medical Comorbidity, OIs and Risk Factors	*Aspergillus* Species	Signs and Symptoms	Site of Invasion	Surgery	Antifungal	Outcome & Comments	Ref.
1999[a]	36	M	0	n/a	n/a	*A fumigatus*	Otalgia, otorrhea, hearing loss, CNVII palsy (partial recovery after 8 mo)	mastoid only	debridement	AmB, ltra	alive (8 mo after surgery, although developed recurrence requiring repeat debridement)	[42]
1999[a]	28	M	28	n/a	n/a	*A fumigatus*	otalgia, otorrhea, CNVII palsy (improved 1 d after surgery)	mastoid only	mastoidectomy, debridement	n/a	death (3 mo)	[42]
1999[a]	36	F	4	n/a	n/a	*A fumigatus*	CNVII palsy	mastoid, exposed dura	mastoidectomy	AmB	death (5 mo due to PCP)	[43]
1999[a]	37	M	6	n/a	n/a	*A fumigatus*	n/a	mastoid, exposed dura	mastoidectomy	AmB×4 wk	n/a	[43]

Abbreviations: AIDS, acquired immune deficiency syndrome; AmB, amphotericin B; ANC, absolute neutrophil count; ART, antiretroviral therapy; AZT, zidovudine; CMV, cytomegalovirus; CMV-R, CMV retinitis; CNS toxo, central nervous system toxoplasmosis; CNVII, cranial nerve 7; f/u, follow-up; Itra, itraconazole; HIV, human immunodeficiency virus; KS, Kaposi sarcoma; MAI, disseminated *Mycobacterium avium-intracellulare*; n/a, not available in report; OI, opportunistic infection; OM, otitis media; PCP, pneumocystis pneumonia; TM, tympanic membrane; TMP/SMX, trimethoprim/sulfamethoxazole; ZDV, zidovudine.

[a] Indicated year of publication when year of case not reported.

[b] CD4 cell count in cells/mm^3; "AIDS" listed when specified in report and when CD4 cell count not reported.

range of clinical signs including proptosis, decreased vision, diplopia, eye pain, lid erythema, and exophthalmos. Among these cases, proptosis, diplopia, and visual impairment are noteworthy signals of orbital apex syndrome, a clinical diagnosis for which invasive fungal sinusitis is an important consideration in the differential diagnosis [11, 21]. Paranasal sinus IA may spread to a variety of intracranial or extracranial sites as shown in our review (Tables 3 and 4).

Among *Aspergillus* mastoiditis cases, otalgia (73%), hearing loss (47%), and otorrhea (40%) were commonly reported symptoms and were likely a reflection of concurrent otitis media as the inciting source for mastoiditis. Facial nerve palsy, a recognized complication of chronic otitis media and mastoiditis given the anatomically traversing path of the facial nerve, also occurred in 60% of evaluable cases and did resolve in some cases [41]. This percentage exceeds the 14%–18% of those with non-HIV-associated bacterial mastoiditis reported to have facial nerve palsy [52, 53]. Intracranial invasion occurred in 53% of cases in our series, which was also higher than in other series (Table 4) [53, 54].

The approach to diagnosis does not differ between HIV-infected and uninfected patients. Radiographic imaging by CT or MRI is necessary both to diagnose invasive sinusitis and determine its extent to guide surgical intervention [1]. However, radiographic findings cannot reliably distinguish between the various causes of invasive sinusitis. Definitive IA requires histopathologic confirmation of hyphal invasion in tissue specimens or growth in culture from a site of disease [1]. Tissue is often obtained by direct endoscopic exam and biopsy of the involved sinus. For mastoiditis, deep cultures, rather than external swabs, are imperative to confirm invasive disease given the frequency of superficial fungal otitis externa [37].

Fungal biomarkers may provide earlier evidence of invasive *Aspergillus* than culture in high-risk patients. However, the urgency of targeted antifungal therapy and surgical debridement currently limits their impact in the management of suspected invasive fungal sinusitis, and most cases in our review temporally preceded the clinical use of biomarkers in the diagnosis of IA. Serum galactomannan antigen is specific for *Aspergillus*, but its use in invasive *Aspergillus* sinusitis has been sparsely evaluated and the test may be insensitive in the condition [36, 55, 56]. Detection of serum (1→3)-β-D-glucan may afford increased sensitivity in detecting fungal invasion but is not specific for *Aspergillus*. Both of these biomarkers were detected in our patient but were not serially monitored given that they were unlikely to change clinical management. Finally, serum or tissue polymerase chain reaction (PCR) is an emerging diagnostic tool that may offer rapid diagnosis with improved sensitivity and specificity. However, its optimal use has not yet been determined and it remains unavailable in most settings [57, 58].

The lack of randomized controlled trials for treatment of IA sinusitis makes the best strategies for managing the disease

Table 3. Summary of Cases of Invasive Aspergillosis of the Paranasal Sinuses in Individuals With HIV Infection (n = 42)

Characteristic[a]	n (%)
Year of case	
1999 and before	38 (90)
2000–2015	4 (10)
Male sex (n = 41)	28 (68)
Age, mean (interquartile range) (n = 41)	36 (32–40)
AIDS diagnosis (n = 41)	40 (98)
CD4 < 50 cells/mm^3 (n = 30)	29 (97)
Antiretroviral therapy not reported	29 (69)
History of AIDS-defining opportunistic infection (n = 38)	28 (74)
Aspergillus species (n = 39)	
Aspergillus fumigatus	37 (95)
Aspergillus flavus	2 (5)
Risk factors for invasive aspergillosis (n = 38)	
Any neutrophil disorder	17 (45)
Medications associated with neutropenia[b]	14 (37)
Neutropenia (≤1000 cells/mm^3)[c]	12 (32)
Corticosteroid use	6 (16)
Chronic sinusitis	6 (16)
Reported marijuana use	4 (11)
Chemotherapy	3 (8)
Prior sinus surgery	3 (8)
Chronic alcohol use	1 (3)
Signs/Symptoms (n = 32)	
Headache	15 (47)
Fever	14 (44)
Pain	13 (41)
Proptosis	12 (38)
Decreased vision	11 (34)
Cranial nerve palsy	7 (22)
Facial or periorbital swelling	7 (22)
Sinus involved (n = 39)	
Multisinus[d]	30 (77)
Maxillary	28 (72)
Ethmoid	28 (72)
Sphenoid	20 (51)
Frontal	17 (44)
Site of Invasion (n = 41)	
Orbit	22 (54)
Frontal lobe	9 (22)
Intracranial or epidura[e]	6 (15)
Cavernous sinus	6 (15)
Temporal lobe/fossa	5 (12)
Optic chiasm	2 (5)
Other[f]	10 (24)
Treatment	
Surgery (n = 39)	32 (82)
Antifungal therapy (n = 38)	37 (97)
Amphotericin B	31 (82)
Itraconazole	14 (37)
Voriconazole	3 (8)
Micafungin	1 (3)
Mortality (n = 41)	33 (80)

Abbreviations: AIDS, acquired immune deficiency syndrome; G-CSF, granulocyte colony-stimulating factor; HIV, human immunodeficiency virus.

[a] Percentages are based on total number of evaluable cases (ie, those reporting data for given variable) denoted (n = __).

[b] Includes ganciclovir, trimethoprim-sulfamethoxazole, zidovudine, or G-CSFs, which may indicate presence of neutropenia.

[c] Includes both reported "neutropenia" and when absolute neutrophil count ≤1000 cells/mm^3.

[d] Multisinus defined as >1 sinus involved in either cranial hemisphere.

[e] Includes intracranial space or brain not further specified in report, and meninges.

[f] Includes pterygopalatine fossa (n = 2, 5%), nasal septum (n = 2, 5%), sella turcica or suprasellar area (n = 2, 5%), hard palate (n = 1, 3%), brain stem (n = 1, 2%), basal ganglia (n = 1, 2%), foramen ovale (n = 1, 2%), middle cranial fossa (n = 1, 2%).

uncertain. Nevertheless, observational studies suggest that early diagnosis, early antifungal therapy, and surgical debridement improve outcome [2, 55, 59, 60]. These findings underscore the importance of pursuing diagnostic imaging and tissue sampling for microbiology whenever invasive fungal sinusitis is suspected. As previously noted, liposomal amphotericin B is recommended as empiric therapy until the diagnosis of mucormycosis is ruled out and the presence of *Aspergillus* is confirmed [1, 46, 47]. However, once *Aspergillus* is confirmed, voriconazole is recommended [1]. Azole-resistance *A fumigatus* has been described outside of HIV and unrelated to prior azole exposure but is uncommon [61]. It remains unclear whether local amphotericin B administration offers any benefit beyond systemic amphotericin B.

In our review, amphotericin B and itraconazole were used in nearly all cases, most of which predated the US Food and Drug Administration (FDA) approval of voriconazole and the publication of treatment guidelines recommending its use in 2002 and 2008, respectively [1]. Novel FDA-approved azole-class antifungals such as posaconazole and isavuconazole offer additional treatment options with the added advantages of anti-Mucorales activity and high oral bioavailability, but they have not been proven superior to voriconazole in the treatment of IA sinusitis. Drug interactions are a particular concern when prescribing azole-class medications to an HIV-infected patient taking ART and should be reviewed beforehand [62]. For example, voriconazole levels decrease significantly when administered with HIV protease inhibitors, and coadministration of voriconazole with ritonavir or cobicistat should be avoided. Coadministration of efavirenz and voriconazole is contraindicated at standard efavirenz dosages due to the concomitant effects of voriconazole increasing efavirenz levels and efavirenz decreasing voriconazole levels. Monitoring of voriconazole levels in such circumstances can be helpful [1, 62]. Echinocandin class antifungals such as caspofungin or micafungin offer additional treatment options in IA while avoiding these drug interactions. Micafungin was initially used as part of combination therapy with voriconazole in our case but was discontinued given the need for prolonged therapy. Although efficacy of this strategy still remains to be established in humans, in vitro studies and animal models suggest that these agents have additive or synergistic effects without antagonism.

The optimal duration of therapy for acute IA sinusitis is not defined. However, prolonged therapy (≥1 year) has been successful and is recommended at minimum through recovery from severe immunosuppression (>200 cells/mm^3 in HIV infection) [1, 31, 63]. The duration of therapy for chronic IA sinusitis in less immunocompromised patients, such as our patient, is also undefined. In such cases, surgical debridement often plays an important role in guiding treatment duration. The use of fungal biomarkers to inform therapeutic response has been used in pulmonary aspergillosis but not sinusitis.

Surgical debridement is a potentially life-saving intervention in patients with IA sinusitis and should be considered as an

Table 4. Summary of Cases of Invasive *Aspergillus* Mastoiditis in Individuals With HIV Infection (n = 17)

Characteristic[a]	n (%)
Year of case	
1999 and before	17 (100)
2000–2015	0 (0)
Male sex	6 (35)
Age, mean (interquartile range)	32 (27–39)
AIDS diagnosis	17 (100)
CD4 < 50 cells/mm^3 (n = 8)	8 (100)
Antiretroviral therapy not reported	12 (71)
History of AIDS-defining opportunistic infection (n = 11)	8 (73)
Aspergillus species	
Aspergillus fumigatus	17 (100)
Risk factors for invasive aspergillosis (n = 11)	
Medications associated with neutropenia[b] (n = 13)	7 (54)
Chronic/recurrent otitis media or otitis externa	6 (55)
Any neutrophil disorder	2 (18)
Neutropenia (≤1000 cells/mm^3)[c]	2 (18)
Corticosteroid use	0 (0)
Chemotherapy	0 (0)
Reported marijuana use	0 (0)
Prior surgery	0 (0)
Signs/Symptoms (n = 15)	
Otalgia	11 (73)
Facial nerve palsy	9 (60)
Hearing loss	7 (47)
Otorrhea	6 (40)
Fever	4 (27)
Headache	3 (20)
Site of Invasion	
Mastoid only	6 (35)
Temporal lobe	5 (29)
Temporal bone or epidura	4 (24)
Cerebellum	3 (18)
Lateral sinus	1 (6)
Treatment	
Surgery (n = 16)	14 (88)
Antifungal therapy (n = 16)	15 (94)
Amphotericin B	12 (75)
Itraconazole	9 (56)
Voriconazole	0 (0)
Mortality (n = 15)	11 (73)

Abbreviations: AIDS, acquired immune deficiency syndrome; G-CSF, granulocyte colony-stimulating factor; HIV, human immunodeficiency virus.

[a] Percentages are based on total number of evaluable cases (ie, those reporting data for given variable) denoted (n = __).

[b] Includes ganciclovir, trimethoprim-sulfamethoxazole, zidovudine, or G-CSFs, which may indicate presence of neutropenia.

[c] Includes both reported "neutropenia" and when absolute neutrophil count ≤1000 cells/mm^3.

adjunct to antifungal therapy whenever possible [1, 2, 55]. Over 80% of patients in our review underwent surgery, which is consistent with other series [2, 55]. Still, although advances in endoscopic techniques have lessened surgical morbidity, extensive debridement may be futile or portend unacceptable morbidity in severely immunocompromised patients or in cases of intracranial involvement. In our review, mortality from paranasal sinus IA was 80% despite most patients undergoing surgery, and 42% of those who did undergo surgery died within 2 weeks of the procedure [16, 17, 21, 22, 24, 25, 27]. Most died from other diseases, and this may also reflect advanced HIV disease before the development of effective ART.

Finally, reversal of immunosuppression is a critical intervention in patients with IA. For the HIV-infected patient, this includes administration of ART [63]. Immune reconstitution inflammatory syndrome has been rarely described in HIV patients and hematopoietic stem cell transplant recipients with pulmonary IA [64–66]. Supplemental therapies to restore the innate immune system of HIV-infected patients such as granulocyte/macrophage colony-stimulating factors were used in 2 cases in our review [20, 23]. Although no data evaluating their efficacy in HIV-associated IA exist, these medications have been shown to restore phagocyte response in HIV-associated neutropenia and have a growing role in treatment of aspergillosis in other immunocompromised populations [1, 67–70].

Multiple series of invasive fungal sinusitis report mortality rates in excess of 50% in immunocompromised populations regardless of the cause of immune compromise [1, 2, 4, 6, 9, 27, 55, 71]. In our review of HIV-infected patients, the mortality was 80% and 73% in paranasal and mastoid sinus IA, respectively. This underscores both the lethal nature of IA sinusitis and the highly vulnerable population in which it occurred. Indeed, nearly all of the individuals in our series had a history of advanced HIV with multiple AIDS-OIs and died without ever receiving effective ART (Tables 3 and 4). As such, AIDS-related morbidity undoubtedly contributed to the high mortality rate in our series and could likely have been reduced with effective ART [6, 12, 16, 17, 30, 34, 41, 43].

The initial case definition of AIDS from 1982 included IA [72]. In 1984, IA was removed from the US Centers for Disease Control and Prevention list of AIDS-defining illnesses because of IA's association with neutrophil (rather than cellular) defects and the low number of reported cases of IA in individuals with HIV [5, 6, 72]. Today, advanced HIV infection is a recognized, but uncommon, risk factor for IA supported by multiple cases in the literature, with the highest risk occurring at CD4 counts <50–100 cells/mm^3 [1, 4, 5, 44]. In our review, a history of AIDS was reported in all but 1 case, and the CD4 cell count was <50 cells/mm^3 in nearly all of the cases in which CD4 counts were reported [31]. Antiretroviral therapy was not reported for 70% of cases. Moreover, classic risk factors for IA (ie, neutrophil disorders, chemotherapy, corticosteroids) were reported in <50% of cases, consistent with other series of HIV patients with primarily pulmonary IA [6, 36].

Still, few individuals with advanced HIV infection develop IA despite ubiquitous environmental exposure to *Aspergillus* [5, 8, 63]. Although the host and pathogen-related factors responsible for this selective predisposition are not fully understood, a variety of HIV-related immune defects that bear relevance to the anti-*Aspergillus* immune defense have been described.

For example, low neutrophil numbers (ie, 500–1000 cells/mm^3) and neutrophil functional defects can impair the ability to restrict tissue invasion of *Aspergillus* hyphae [73, 74]. Historically, neutropenia was documented over the course of HIV infection in 20%–50% of patients, either as a direct consequence of HIV-related myelosuppression or myelosuppressive drugs such as zidovudine, trimethoprim-sulfamethoxazole, or ganciclovir [70, 75, 76]. However, these neutropenic episodes are often mild, brief, self-limited, and uncomplicated [70], and neutrophil function may be retained. However, HIV-related neutrophil functional defects have also been identified that persist independent of neutropenia and the response to ART. These defects include compromised neutrophil recruitment and chemotaxis as a result of deficient interleukin-8 production and response by neutrophils [77, 78], impaired complement receptor function [78], defective monocyte/macrophage phagocytosis [69], and altered neutrophil development in the bone marrow [77]. Impaired cytokine production belonging to the Th1 immune response, such as interferon gamma, may further impair neutrophil activation and oxidative metabolism, whereas opsonization of invading conidia may be reduced in tissue with poor complement and opsonin supply [73]. Polymorphisms in Toll-like receptors, dectin, and signal transduction molecules may also increase the risk of IA in patients with HIV-driven immunodysregulation. It is unknown whether the immunorestorative effects of ART will completely reverse these effects, but it is notable that the number of reported cases declined significantly after 1999, when effective ART use increased.

Our case of chronic IA sinusitis in a woman with CD4 > 200 cells/mm^3 is also a reminder that IA can present in various body sites across the spectrum of host immune function. Chronic pulmonary aspergillosis, for example, is known to occur in immunocompetent patients with or without HIV infection who have cavitary lung disease as sequelae of pulmonary tuberculosis (PTB) [79]. In the context of the HIV population, the number of PTB-coinfected individuals at risk of developing a pulmonary aspergilloma is substantial when one considers that approximately 5% of all individuals with PTB cavities will develop an aspergilloma. Indeed, approximately 1 million of the estimated 9 million cases of PTB in 2014 occurred in HIV-infected people, likely resulting in approximately 50 000 new cases of HIV-associated pulmonary aspergillosis regardless of the degree of HIV-related immunocompromise [80]. Moreover, most cases of chronic pulmonary aspergillosis complicating PTB are thought to occur in Africa and South-East Asia where underdiagnosis of aspergillosis is more likely to occur.

The results of our literature are limited by our nonsystematic approach and reliance on published cases, which may be subject to reporting bias. That most cases occurred before the availability of effective ART or voriconazole likely limits the generalizability of the results in the present era.

CONCLUSIONS

Invasive *Aspergillus* sinusitis is an opportunistic infection with low incidence but high mortality in individuals with advanced HIV infection. A high proportion of these patients harbor traditional risk factors for invasive aspergillosis. However, invasive aspergillosis may also occur in those with normal or minimally compromised immunity. Further research is needed to understand the immune defects in HIV that predispose to invasive aspergillosis and the optimal management strategies for the disease.

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